II. REMARKS

Formal Matters

Claims 1-26 are pending after entry of the amendments set forth herein.

Claims 1-26 were examined. Claims 1-3, 10, 12-19 and 26 were rejected. Claims 4-9, 11, and 20-25 were withdrawn from consideration.

Claims 1, 17, and 26 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendments to claims 1, 17, and 26 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: page 8, lines 28-30. Accordingly, no new matter is added by these amendments.

Please replace claims 1, 17, and 26 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Rejection under 35 U.S.C. §112, second paragraph

Claims 2 and 3 were rejected under 35 U.S.C. §112, first paragraph, as allegedly indefinite.

The Office Action stated that the term "selective for EGF-R" is vague and indefinite. Applicants respectfully traverse the rejection.

The term "selective for EGF-R" in the phrase "wherein said EGF-R antagonist is a kinase inhibitor selective for EGF-R" is a term well understood in the art, and refers to EGF-R antagonists that have a selective action on EGF-R as compared to other tyrosine kinases. Specification, page 9, lines 27-29. As shown in the Examples, tyrosine kinase inhibitors selective for EGF-R such as BIBX1522 and AG1478, *but not a selective PDGF kinase inhibitor*, were effective in reducing MUC5AC synthesis Specification, page 40, lines 12-20; and page 69, lines 8-13. Accordingly, the term is clear, and claims 2 and 3 need not be amended.

Applicants submit that the rejection of claims 2 and 3 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1-3, 10, 12-19, and 26 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking written description. Claims 1-3, 10, 12-19, and 26 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

Written description

The Office Action stated that the specification and claims do not indicate what distinguishing attributes are concisely shared by the members of the genus comprising EGF-R antagonists; the specification and claims do not describe elements which are essential to the genus comprising such antagonists; and the scope of the claims includes numerous structural variants. The Office Action further stated that the specification fails to teach or adequately describe a representative number of species, and concluded that Applicants were not in possession of the claimed genus. Applicants respectfully traverse the rejection.

The specification provides adequate written description for EGF-R antagonists.

The specification provides ample description of EGF-R antagonists. Specification, page 7, line 21 to page 8, line 23. Many of the EGF-R antagonists discussed in the specification are known to those skilled in the art. The general classes of EGF-R antagonists described in the specification include tyrosine kinase inhibitors, antibodies that bind a factor that stimulates EGF or EGF-R production, e.g., an antibody to TGF-α.

The specification provides working examples of at least three different EGF-R antagonists: two different tyrosine kinase inhibitors, as well as an antibody to TGF-α. For example, the specification provides working examples that BIBX1522, a tyrosine kinase inhibitor that is an EGF-R antagonist, inhibits MUC5AC production in cultured cells *in vitro* and inhibits mucus hypersecretion *in vivo*. Specification, e.g., Example 1. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. AG1478 and BIBX1522 inhibit goblet cell hyperplasia. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced stimulation of the EGF-R and reduced production of goblet cells. Specification, e.g., Example 3.

The Office Action stated that the specification does not indicate what distinguishing attributes are concisely shared by members of "EGF-R antagonists." However, there is no statutory requirement for such. To satisfy the written description requirement of 35 U.S.C.§112, first paragraph, Applicants are only required to describe identifying characteristics or a representative number. Applicants have done so. An identifying characteristic of an EGF-R antagonist is that it functions as an EGF-R antagonist. Applicants have described this in detail and have provided a description of how to determine whether a compound functions as an EGF-R antagonist. Furtherpmore, Applicants have provided a description of a number of EGF-R antagonists, many of which are already known in the art, and have provided working examples showing the effects of three different EGF-R antagonists.

Furthermore, the claims recite that the EGF-R antagonist is present in an amount "sufficient to reduce goblet cell hyperplasia." Thus, the claim language excludes EGF-R antagonists that do not reduce goblet cell hyperplasia.

The Office Action stated that the specification fails to teach or adequately describe a representative number of species of EGF-R antagonists. However, the specification states that EGF-R antagonists include antibodies that block binding of an EGF-R antagonist to an EGF-R, thereby preventing activation of the receptor, and the specification provides references describing such antibodies. Specification, page 7, lines 25-29. The specification further states that EGF-R antagonists include tyrosine kinase inhibitors, and provides a list of several such inhibitors. Specification, page 8, lines 11-22.

In view of the above-discussed disclosure, those skilled in the art would reasonably expect that Applicants had, at the time the instant application was filed, possession of the invention as claimed. Those skilled in the art would reasonably expect that other EGF-R antagonists would reduce goblet cell hyperplasia.

Enablement

The Office Action stated that the claims are enabling for a method of reducing goblet cell hyperplasia in an airway of an individual, comprising the administration of the EGF-R antagonist BIBX1522 prior to induction of EGF-R. The Office Action stated that the specification is not enabling for methods of reducing goblet cell hyperplasia in an individual's airways or treating nasal polyps

comprising the administration of any EGF-R antagonist via any mode of administration. Applicants respectfully traverse the rejection.

EGF-R antagonists

As discussed above, the specification provides ample description of a number of EGF-R antagonists. The specification provides ample description, including working examples, of how to determine whether a given EGF-R antagonist will function to reduce goblet cell hyperplasia. Furthermore, the specification provides **working examples** of *in vitro* and *in vivo* inhibition of mucin expression and airway mucus hypersecretion (and therefore reducing goblet cell hyperplasia) using BIBX1522, an EGF-R tyrosine kinase inhibitor. The specification also provides working examples of two additional EGF-R antagonists. The specification further provides a working example showing that AG1478, another tyrosine kinase inhibitor that is an EGF-R antagonist, prevented MUC5AC synthesis induced by an activator of EGF-R, and inhibited EGF-R phosphorylation. Specification, e.g., Example 2. The specification further provides a working example showing that a TGF-α neutralizing antibody reduced stimulation of the EGF-R and reduced production of goblet cells. Specification, e.g., Example 3.

Thus, the specification provides three working examples of EGF-R antagonists that are efficacious in reducing goblet cell hyperplasia.

Route of administration

The Office Action stated that the specification is not enabling because practice of the invention would require the *de* novo determination of accessible target sites, modes of delivery, and formulations to target appropriate cells and/or tissues. However, in reducing goblet cell hyperplasia, and treating nasal polyps, the target cell population is in the airways. Thus, there is no need to determine accessibility of target sites, because such is already known. Furthermore, Applicants showed that systemic delivery of BIBX1522 reduces airway goblet cell hyperplasia. Thus, those skilled in the art would reasonably expect that the same EGF-R antagonist, when administered by other routes, e.g., via inhalation, would be efficacious, because administration by inhalation is administration directly at the site of the target cells.

Furthermore, the publication Takeyama et al. (2001) *Am. J. Physiol. Lung Cell Mol. Physiol.* 280:L165-L172, a copy of which is provided herewith as Exhibit 1, shows that inhalation of cigarette

smoke stimulates mucin production (resulting from goblet cell hyperplasia) in rats *in vivo*, and that the increase in mucin production was prevented by intratracheal instillation of a selective EGFR tyrosine kinase inhibitor in a dose-dependent fashion. Intratracheal instillation in experimental animals is a well-accepted model of airway delivery. Thus, EGFR antagonists, when administered by inhalation, reduce goblet cell hyperplasia.

Timing of administration

The Office Action stated that the specification is enabling only for reduction of goblet cell hyperplasia comprising administration of BIBX1522 prior to induction of goblet cell hyperplasia, and prior to EGF-R induction. However, the Office Action has not provided any reasoning as to why one skilled in the art would not expect that administration of an EGF-R antagonist would be effective in reducing goblet cell hyperplasia, and therefore in treating nasal polyps, even after induction of EGF-R.

Furthermore, Applicants note that when an EGFR is stimulated, tyrosine kinase phosphorylation occurs rapidly, e.g., within minutes. Similarly, after acute stimulation of EGFR, the phosphorylation process is turned off rapidly. In chronic inflammation, chronic EGFR activation results in chronic mucus overproduction. Interruption of the EGFR cascade thus initiates an interference with mucin production in a very short period of time, and the effect will remain as long as the inhibitor therapy is continued. Accordingly, one skilled in the art would reasonably expect that administration of an EGFR antagonist after EGFR induction reduces goblet cell hyperplasia.

Conclusion as to rejection under 35 U.S.C.§112, first paragraph

As discussed above, the specification provides ample description of EGF-R antagonists, provides ample description of assays for determining whether an EGF-R antagonist reduces goblet cell hyperplasia, and provides working examples of different EGF-R antagonists that reduce goblet cell hyperplasia. Furthermore, given the fact that intraperitoneal administration was shown to be effective in reducing goblet cell hyperplasia in the airways, one skilled in the art would reasonably expect that other routes of administration, including inhalation routes, are also effective.

Nevertheless, and solely in the interest of expediting prosecution, the claims are amended to recite that the EGF-R antagonist binds the EGF-R.

Applicants submit that the rejection of claims 1-3, 10, 12-19, and 26 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSF085CIP.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Apr. 23, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please enter the amendments to claims 1, 17, and 26, as shown below.

1. (Amended) A method of reducing goblet cell hyperplasia in an airway of an individual, comprising:

administering [a therapeutically effective amount of] an epidermal growth factor receptor (EGF-R) antagonist that binds the EGF-R to a patient suffering from airway hypersecretion of mucus due to airway goblet cell hyperplasia in an amount effective to reduce goblet cell hyperplasia.

17. (Amended) A pharmaceutical formulation for reducing [of] goblet cell hyperplasia in an airway, comprising:

a therapeutically effective amount of an epidermal growth factor receptor (EGF-R) antagonist that binds an EGF-R in a dose sufficient to reduce goblet cell hyperplasia in an airway;

and a pharmaceutically acceptable carrier.

26. (Amended) A method of treating nasal polyps, comprising administering [a therapeutically effective amount of] an epidermal growth factor receptor (EGF-R) antagonist that binds an EGF-R to a patient suffering nasal polyps in an amount effective to reduce goblet cell hyperplasia.